NCCN National Comprehensive Cancer Network®

The NCCN

Testicular Cancer

Clinical Practice Guidelines in Oncology™

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Overview

An estimated 8090 new cases of testicular cancer will be diagnosed in the United States in 2008.[1] Germ cell tumors (GCTs) comprise 95% of malignant tumors arising in the testes. These tumors also occur occasionally in extragonadal primary sites, but they are still managed the same as testicular GCTs. Although GCTs are relatively uncommon tumors that comprise only 2% of all human malignancies, they constitute the most common solid tumor in men between the ages of 15 and 34 years. In addition, the worldwide incidence of these tumors has more than doubled in the past 40 years.

Several risk factors for GCT development have been identified, including prior history, positive family history, cryptorchidism, testicular dysgenesis, and

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Key Words

NCCN Clinical Practice Guidelines, testicular cancer, germ cell tumors, alpha-fetoprotein, lactate dehydrogenase, human chorionic gonadotropin, cisplatin, seminoma, nonseminoma

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NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Testicular Cancer Guidelines Panel

At the beginning of each NCCN guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Testicular Cancer Guidelines Panel members can be found on page 693. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at www.nccn.org.)

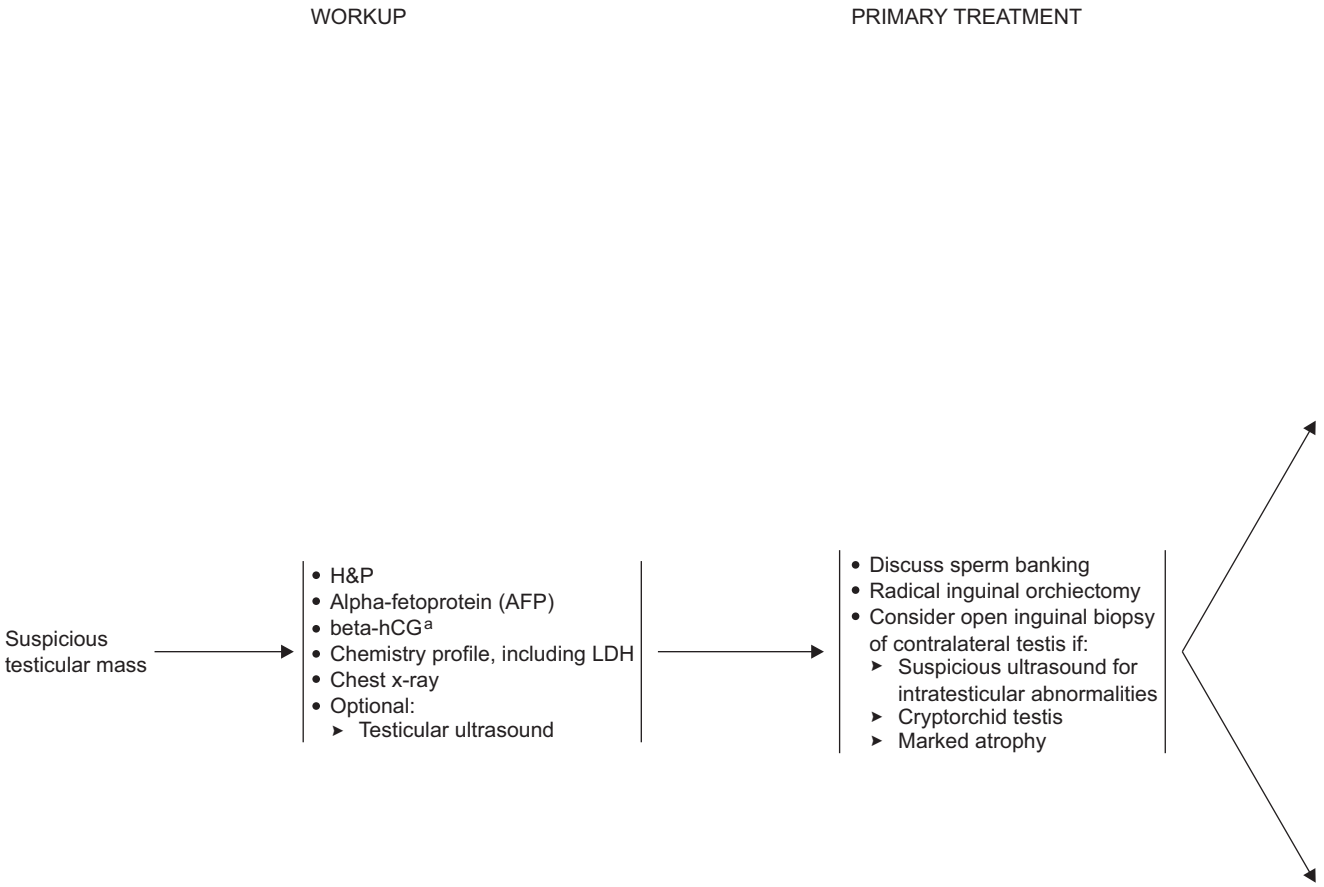
These guidelines are also available on the Internet. For the latest update, please visit www.nccn.org.

Klinefelter's syndrome. GCTs are classified as seminoma or nonseminoma. Nonseminomatous tumors often include multiple cell types, including embryonal cell carcinoma, choriocarcinoma, yolk-sac tumor, and teratoma. Teratomas are considered to be either mature or immature depending on whether adult-type differential cell types or partial somatic differentiation, similar to that present in the fetus, is found. Rarely, a teratoma histologically resembles a somatic cancer, such as sarcoma or adenocarcinoma, and is then referred to as a teratoma with malignant transformation.

The serum tumor markers alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), and human chorionic gonadotropin (hCG) are critical in diagnosing the presence of tumors, determining prognosis, and assessing treatment outcome. These should be determined before, during, and after treatment and throughout the follow-up period. AFP is a serum tumor marker produced by nonseminomatous cells (embryonal carcinoma, yolk-sac tumor) and may be seen at any stage. The approximate half-life of AFP is 5 to 7 days. A nonseminoma, therefore, is associated with elevated serum concentrations of AFP. An elevated serum concentration of hCG, which has a half-life of approximately 1 to 3 days, may also be present with seminomatous and nonseminomatous tumors. Seminomas are occasionally associated with an elevated serum concentration of hCG but not an elevated concentration of AFP.

Nonseminoma is the more clinically aggressive tumor. When both a seminoma and elements of a

Text continues on p. 686



[a] Quantitative analysis of beta subunit.

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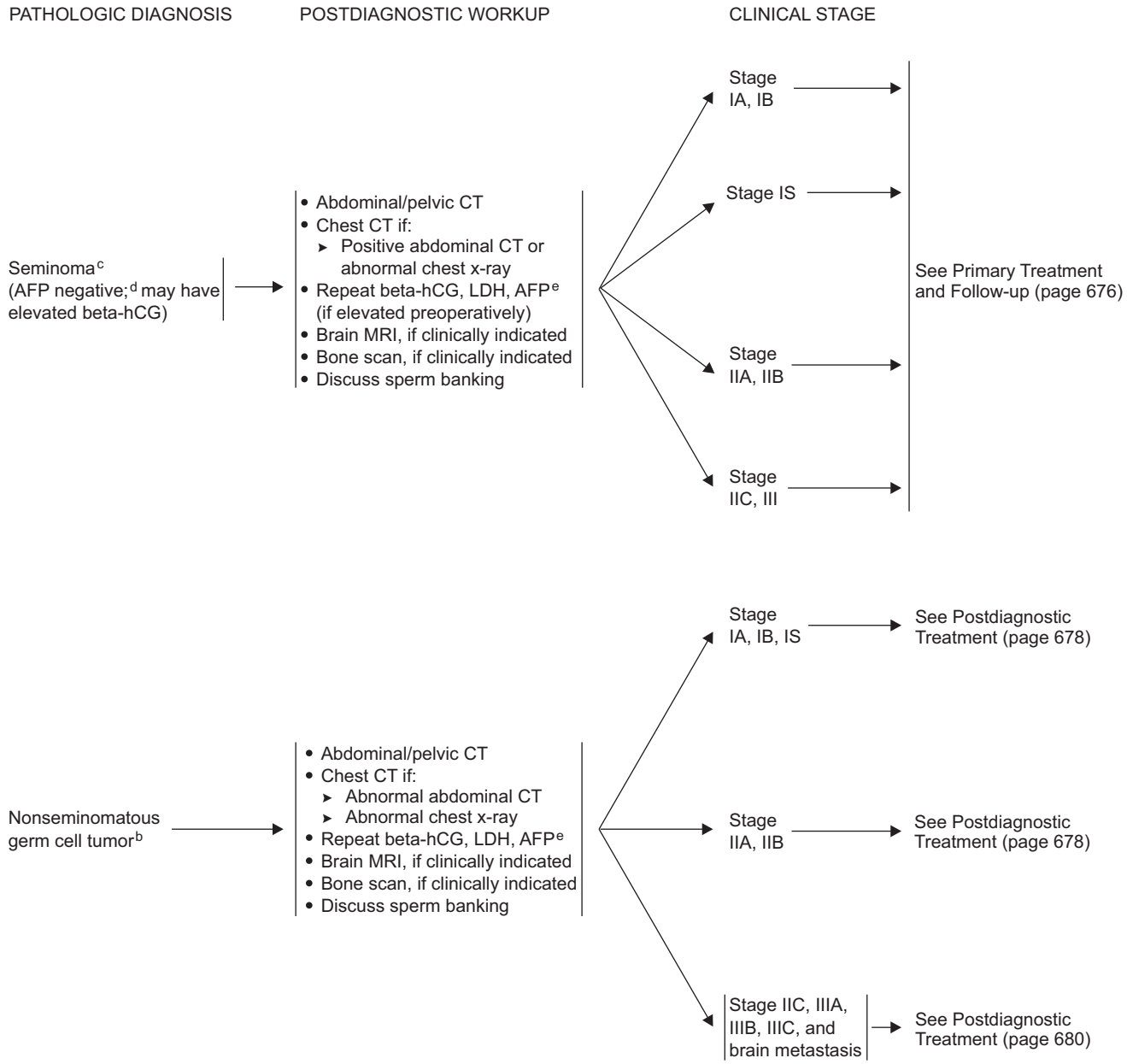
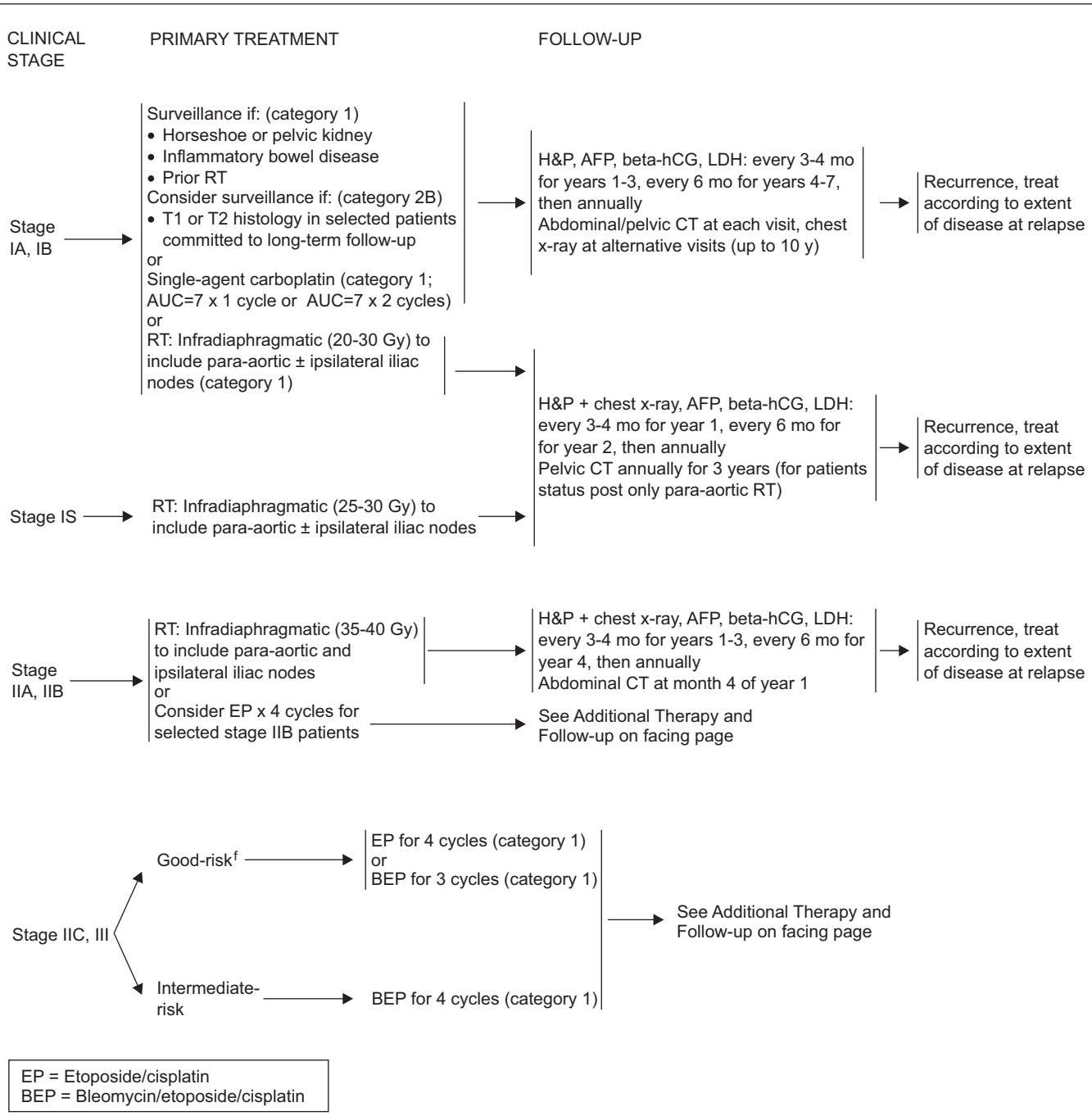
Testicular Cancer Version 2:2009



[b]This includes seminoma histology with elevated AFP.
[c]Mediastinal seminoma should be treated as good risk nonseminomatous germ cell tumor with etoposide/cisplatin for 4 cycles or bleomycin/etoposide/cisplatin for 3 cycles
[d]If positive, treat as nonseminoma.
[e]Elevated values should be followed with repeated determination to allow precise staging.



[f] See Risk Classification (page 683).

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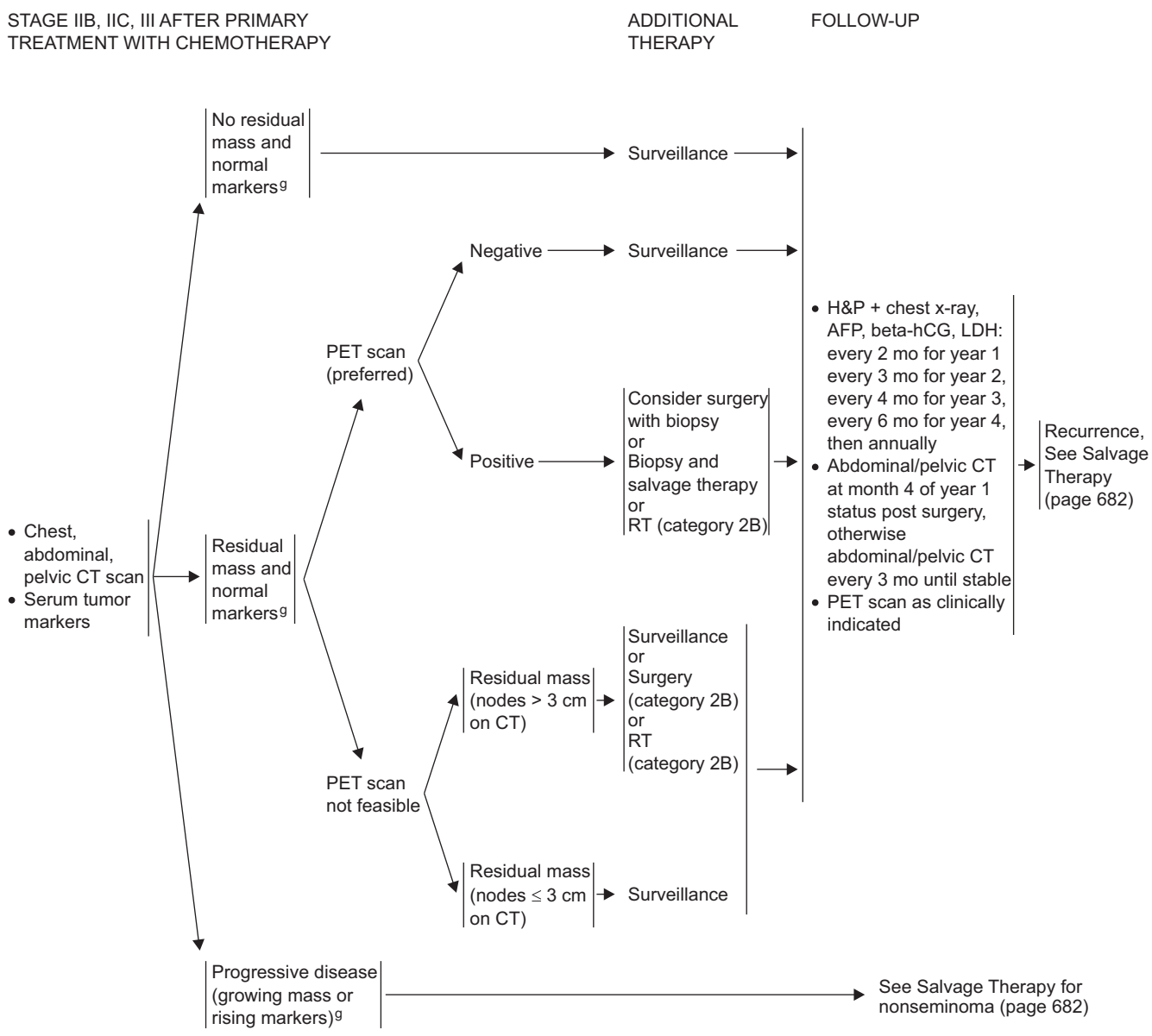
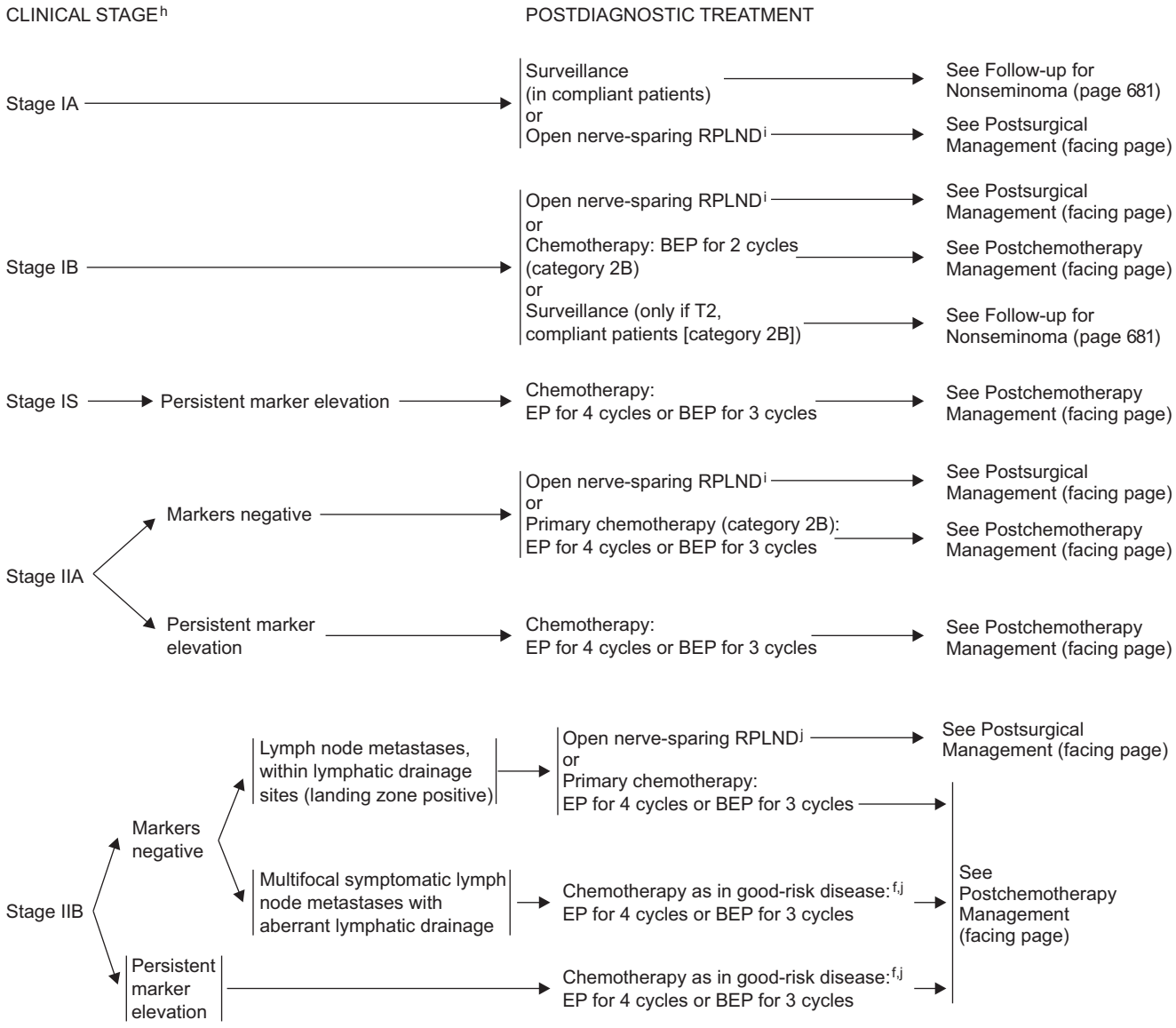


[g]For persistent elevated beta-hCG which is not rising, repeat serial markers, testosterone suppression test, and consider a PET scan.



The EP and BEP chemotherapy regimens have shown survival advantage in randomized clinical trials and may be considered as category 1 compared with other chemotherapy regimens.

EP = Etoposide/cisplatin
BEP = Bleomycin/etoposide/cisplatin
RPLND = Retroperitoneal lymph node dissection

[f] See Risk Classification (page 683).
[h] Treatment may be initiated before histology for patients with rising markers and a deteriorating clinical situation.
[i] Surgery is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).
[j] See Primary Chemotherapy Regimens for Metastatic Germ Cell Tumors (page 684).

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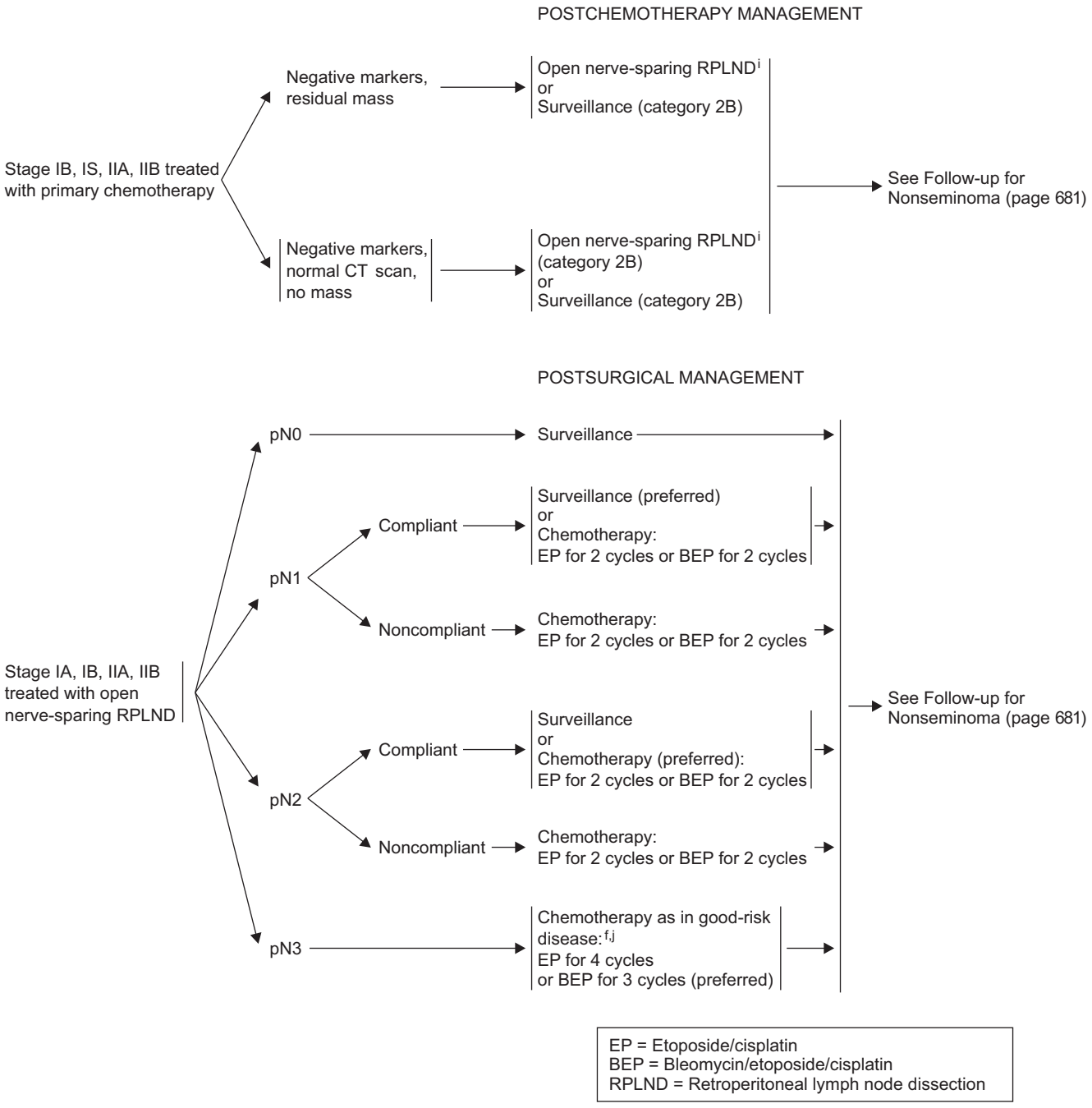
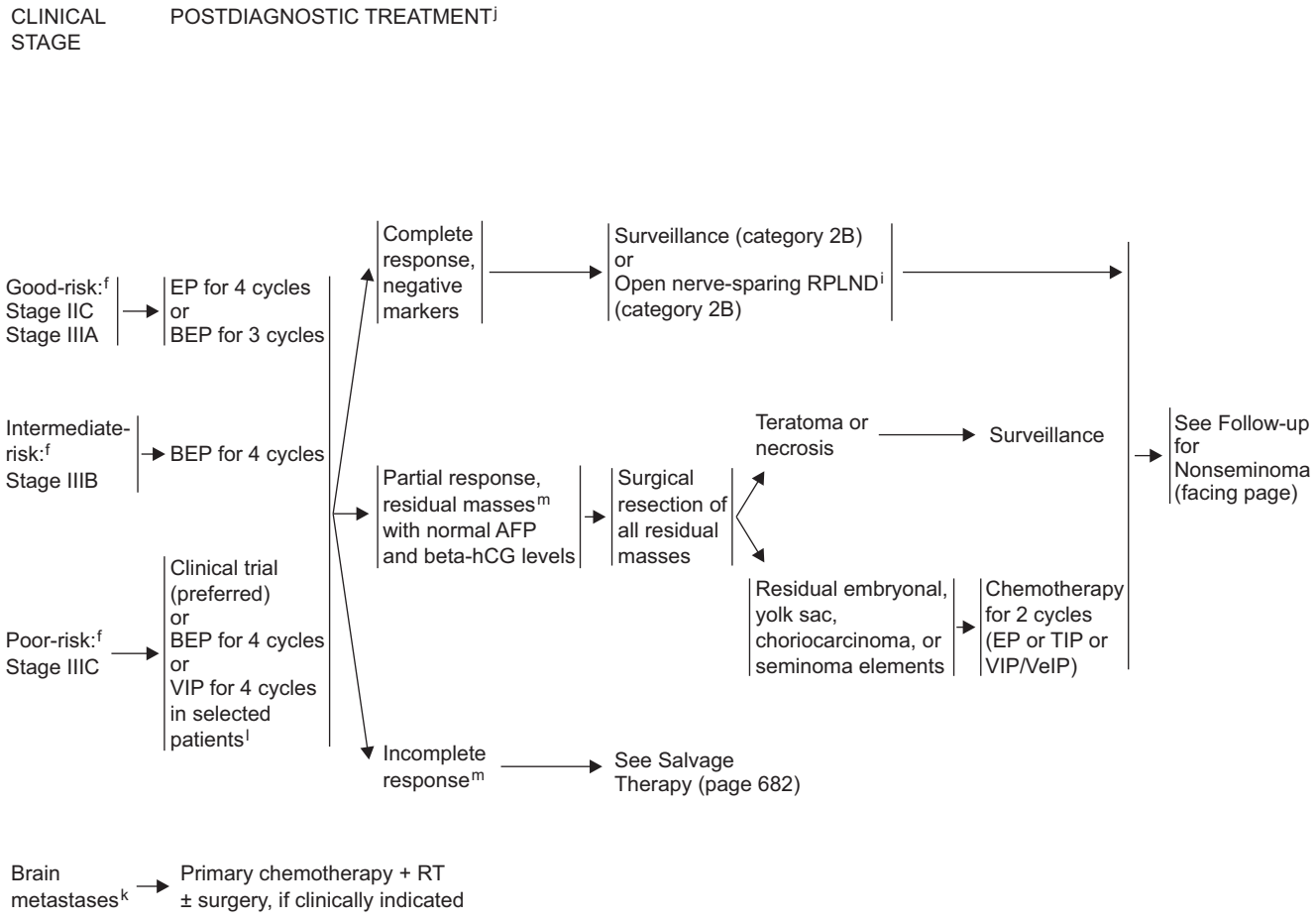


[f] See Risk Classification (page 683).
[i] Surgery is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).
[j] See Primary Chemotherapy Regimens for Metastatic Germ Cell Tumors (page 684).



The EP and BEP chemotherapy regimens have shown survival advantage in randomized clinical trials and may be considered as category 1 compared with other chemotherapy regimens.

EP = Etoposide/cisplatin
BEP = Bleomycin/etoposide/cisplatin
TIP = Paclitaxel/ifosfamide/cisplatin
VeIP = Vinblastine/ifosfamide/cisplatin
VIP = Etoposide/ifosfamide/cisplatin
RPLND = Retroperitoneal lymph node dissection

[f] See Risk Classification (page 683).
[i] Surgery is recommended within 4 weeks of CT scan and 7-10 days of markers (category 2B).
[j] See Primary Chemotherapy Regimens for Metastatic Germ Cell Tumors (page 684).
[k] Patients should undergo adequate treatment for brain metastases, in addition to cisplatin-based chemotherapy.
[l] Patients who may not tolerate bleomycin.
[m] There is limited predictive value for PET scan for residual masses.

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FOLLOW-UP FOR NONSEMINOMA

Surveillance for Stage IA, IB Testicular Cancer

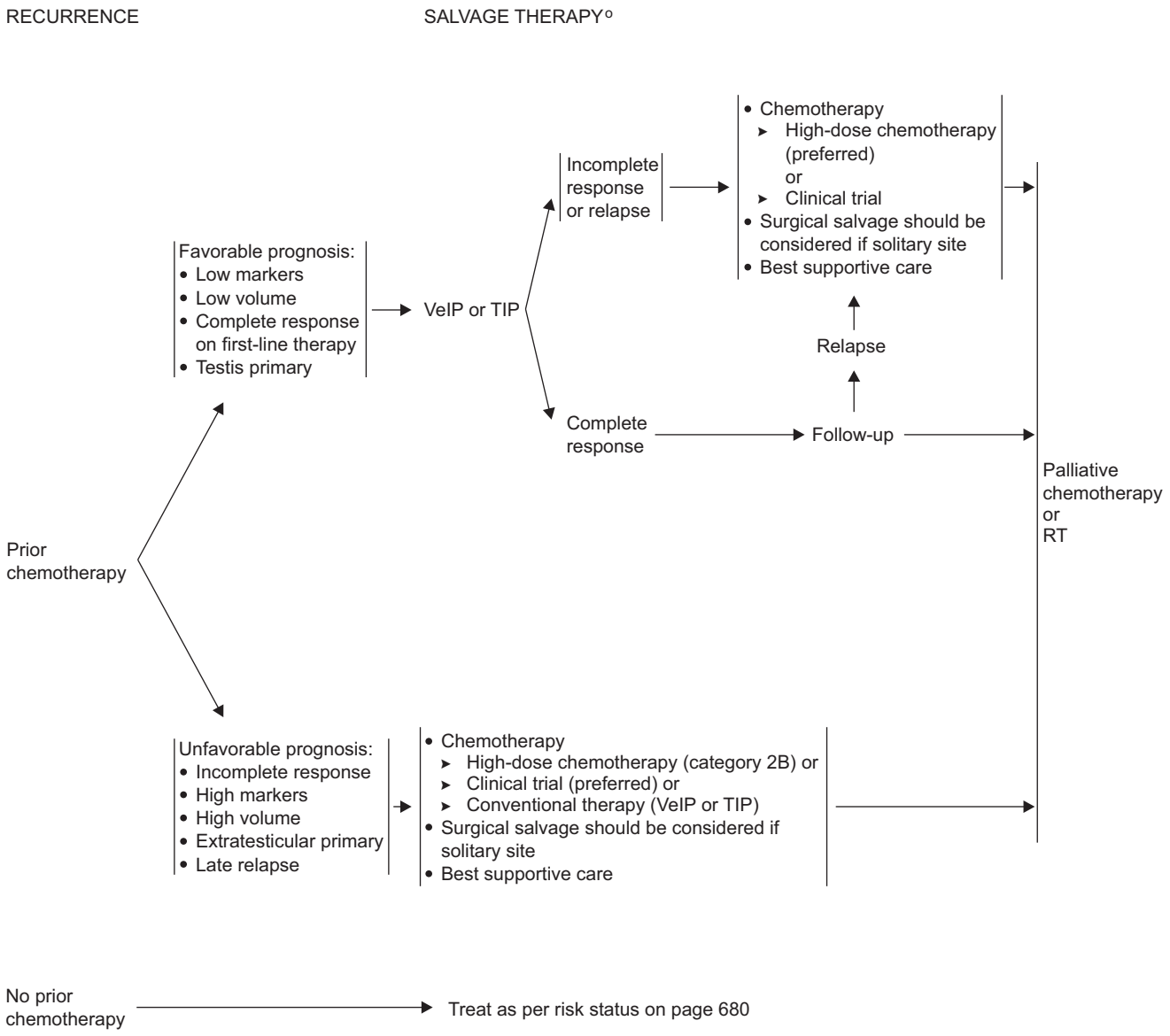
Year	Months Between Visits, Markers, Chest X-Ray	Months Between Abdominal/Pelvic CT
1	1-2	2-3
2	2	3-4
3	3	4
4	4	6
5	6	12
6+	12	12

Surveillance After Complete Response to Chemotherapy and/or RPLND

Year	Months Between Visits, Markers, Chest X-Ray (Category 2B for Chest X-Ray Frequency)	Months Between Abdominal/Pelvic CT[n]
1	2-3	6
2	2-3	6-12
3	4	12
4	4	12
5	6	12
6+	12	12-24

Recurrence, See Salvage Therapy (page 682)

[n]CT scans apply only to patients treated with chemotherapy. Patients status post-RPLND, a postoperative baseline CT scan is recommended.



VeIP = Vinblastine/ifosfamide/cisplatin
TIP = Paclitaxel/ifosfamide/cisplatin

[o]See Salvage Chemotherapy Regimens for Metastatic Germ Cell Tumors (page 685).

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RISK CLASSIFICATION[1]

Risk Status	Nonseminoma	Seminoma
Good-risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Good markers - all of: AFP < 1000 ng/mL hCG < 5000 IUu/L LDH < 1.5 x upper limit of normal	Any primary site and No nonpulmonary visceral metastases and Normal AFP Any HCG Any LDH
Intermediate-risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Intermediate markers- any of: AFP 1000-10,000 ng/ mL hCG 5000-50,000 IU/L LDH 1.5-10 x upper limit of normal	Any primary site and Nonpulmonary visceral metastases and Normal AFP Any HCG Any LDH
Poor-risk	Mediastinal primary tumor or Nonpulmonary visceral metastases or Poor markers - any of: AFP > 10,000 ng/mL hCG > 50,000 IU/L LDH > 10 x upper limit of normal	No patients classified as poor prognosis

Source: International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 1997;15:594-603. Reprinted with permission of the American Society of Clinical Oncology.

[1] Markers used for risk classification are post-orchiectomy.

PRIMARY CHEMOTHERAPY REGIMENS FOR METASTATIC GERM CELL TUMORS

Tumor Status	Regimen
Previously untreated, good-risk	(EP) Etoposide, 100 mg/m^2 IV daily for 5 days, + cisplatin, 20 mg/m^2 IV daily for 5 days, for 4 cycles administered at 21-day intervals[1] or (BEP) Etoposide, 100 mg/m^2 IV daily for 5 days, cisplatin, 20 mg/m^2 IV daily for 5 days, + bleomycin, 30 units IV weekly on days 1, 8, 15* for 3 cycles administered at 21-day intervals[2]
Tumor Status	**Regimen**
Previously untreated, intermediate-, or poor-risk	(BEP) Etoposide, 100 mg/m^2 IV daily for 5 days, cisplatin, 20 mg/m^2 IV daily for 5 days, + bleomycin, 30 units IV weekly on days 1, 8, 15* for 4 cycles administered at 21-day intervals[2] or (VIP) Etoposide 75 mg/m^2 daily for 5 days, ifosfamide 1200 mg/m^2 daily for 5 days, mesna 120 mg/m^2 slow IV push is given before ifosfamide on day 1, followed by 1200 mg/m^2 continuous infusion on days 1 through 5, cisplatin 20 mg/m^2 on days 1 through 5[3]

*Some NCCN Institutions administer bleomycin on a 2, 9, 16 schedule.

[1] Xiao H, Mazumdar M, Bajorin DF, et al. Long-term follow-up of patients with good-risk germ cell tumors treated with etoposide and cisplatin. J Clin Oncol 1997;15:2553-2558.
[2] Saxman SB, Finch D, Gonin R, Einhorn LH. Long-term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide, and cisplatin in favorable-prognosis germ-cell tumors: The Indiana University Experience. J Clin Oncol 1998;16:702-706.
[3] Nichols CR, Catalano PJ, Crawford ED, et al. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. J Clin Oncol 1998;16:1287-1293.

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SALVAGE CHEMOTHERAPY REGIMENS FOR METASTATIC GERM CELL TUMORS

Tumor Status	Regimen
Previously treated, salvage therapy	(VeIP) Vinblastine 0.11 mg/kg IV per day for 2 days, ifosfamide 1200 mg/m^2 IV daily for 5 days, mesna 400 mg/m^2 IV every 8 h x 5 days, and cisplatin 20 mg/m^2 IV daily for 5 days[1] or (TIP) Paclitaxel 250 mg/m^2 IV day 1, followed by ifosfamide 1500 mg/m^2 and cisplatin 25 mg/m^2 IV daily on days 2-5, mesna 500 mg/m^2 IV before, and then 4 and 8 h after each dose of ifosfamide[2]

Palliative, second-line salvage therapy	Regimen
	(GEMOX) Gemcitabine 1000 mg/m^2 IV on days 1 and 8, followed by oxaliplatin 130 mg/m^2 IV on day 1 administered every 3 weeks[3,4]
	(GEMOX) Gemcitabine 1250 mg/m^2 IV on days 1 and 8, followed by oxaliplatin 130 mg/m^2 IV on day 1 administered every 3 weeks[5]

[1] Loehrer PJ Sr, Lauer R, Roth BJ, et al. Salvage therapy in recurrent germ cell cancer: ifosfamide and cisplatin plus either vinblastine or etoposide. Ann Intern Med 1988;109:540-546.
[2] Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol 2005;23:6549-6555.
[3] Pectasides D, Pectasides M, Farmakis D, et al. Gemcitabine and oxaliplatin (GEMOX) in patients with cisplatin-refractory germ cell tumors: a phase II study. Ann Oncol 2004;15:493-497.
[4] Kollmannsberger C, Beyer J, Liersch R, et al. Combination chemotherapy with gemcitabine plus oxaliplatin in patients with intensively pretreated or refractory germ cell cancer: a study of the German Testicular Cancer Study Group. J Clin Oncol 2004;22:108-114.
[5] De Giorgi U, Rosti G, Aieta M, et al. Phase II study of oxaliplatin and gemcitabine salvage chemotherapy in patients with cisplatin-refractory nonseminomatous germ cell tumor. Eur Urol 2006;50:893-894.

Text continued from p. 673

nonseminoma are present, management follows that for a nonseminoma. Therefore, the diagnosis of a seminoma is restricted to pure seminoma histology and a normal serum concentration of AFP.

More than 90% of patients diagnosed with GCTs are cured, including 70% to 80% of patients with advanced tumors who are treated with chemotherapy. A delay in diagnosis correlates with a higher stage at presentation. Standard therapy has been established at essentially all stages of management and must be closely followed to ensure the potential for cure.

Clinical Presentation

A painless solid testicular mass is pathognomonic for testicular tumor. More often, patients present with testicular discomfort or swelling suggestive of epididymitis or orchitis. A trial of antibiotics may be given in this circumstance, but persistent tenderness, swelling, or any palpable abnormality warrants further evaluation using testicular ultrasound. Although testicular ultrasound is optional if the diagnosis is obvious from the physical examination, it is performed in most instances to define the lesion (see page 674).

If an intratesticular mass is identified, further evaluation includes measurement of the serum concentrations of AFP, LDH, and beta-hCG and a chest radiograph. Elevated values of AFP, LDH, or beta-hCG should be followed up with repeated tests to allow precise staging. Inguinal orchiectomy is considered the primary treatment for most patients who present with a suspicious testicular mass.[2] If a GCT is found, an abdominopelvic CT scan is performed. Serum concentrations of hCG and LDH may be elevated in patients with seminoma. An elevated AFP level indicates nonseminoma, and the patient should be managed accordingly.

A chest CT may be indicated if the abdominopelvic CT shows retroperitoneal adenopathy or the chest radiograph shows abnormal results. An open inguinal biopsy of the contralateral testis is not routinely performed, but can be considered when a cryptorchid testis or marked atrophy is present.[3] Biopsy may also be considered if a suspicious intratesticular abnormality, such as a hypoechoic mass or macrocalcifications, is identified on ultrasound. In contrast, if microcalcifications without any other abnormality can be observed, testicular biopsy is not necessary.

These studies, and others as clinically indicated, determine the clinical stage and direct patient management. If clinical signs of metastases are present, MRI of the brain and bone scanning are indicated (see page 675).

Further management is dictated by histology, a diagnosis of seminoma or nonseminoma, and stage (see staging table, available online, in these guidelines, at www.nccn.org [ST-1]). Patients should consider sperm banking before undergoing any therapeutic intervention that may compromise fertility, including radiation therapy, surgery, and chemotherapy.

Seminoma

The risk classification for seminoma is defined in the algorithm (see page 683).

Stages IA and IB

Patients with disease in stages IA and IB are treated with radiation (20–30 Gy) to the infradiaphragmatic area, including para-aortic lymph nodes with or without radiation to the ipsilateral ileoinguinal nodes.[4] Prophylaxis to the mediastinum is not provided, because relapse rarely occurs at this site. A single dose of carboplatin was also investigated as an alternative to radiation therapy. Oliver et al.[5] reported on the results of a trial that randomized 1477 patients with stage I testicular cancer to undergo either radiotherapy or 1 injection of carboplatin. In the study, carboplatin was administered at a dose of area under the curve (AUC) x 7 (area under the dose–time concentration curve). The doses were given intravenously and calculated by a formula based on the AUC estimate of drug disappearance from the body. The dose was calculated using the formula 7 x (glomerular filtration rate + 25) mg. With a median follow-up of 4 years, the relapse-free survivals for both groups were similar.

Because late relapses and secondary GCTs can occur beyond 5 and 10 years, the authors continued the follow-up of these patients. The updated follow-up results of 1148 patients were reported at the 2008 ASCO Annual Meeting.[6] In an intent-to-treat analysis, the relapse-free rates at 5 years were 94.7% for the carboplatin arm and 96% for the radiotherapy arm (hazard ratio [HR], 1.25; P = .37). A significant difference was seen in the rate of new GCTs (2 on carboplatin vs. 15 on radiation therapy), resulting in an HR of 0.22 (95% CI, 0.05, 0.95; P = .03). The authors

concluded that a single dose of carboplatin is less toxic and just as effective in preventing disease recurrence as adjuvant radiotherapy in men with stage I seminoma after orchiectomy.

The NCCN panel now recommends a single dose of carboplatin (category 1) as an alternative to radiation therapy for patients with stages IA and IB disease. Between 15% and 20% of patients with seminoma experience relapse during surveillance if they do not undergo adjuvant radiotherapy after orchiectomy.[7] The median time to relapse is approximately 12 months, but can occur more than 5 years after orchiectomy.

Because both radiation and chemotherapy can lead to late morbidity, surveillance for stage I seminoma is an option for managing stage I seminoma (category 1). In particular, observation may be offered to selected patients with T1 or T2 disease (category 2B) who are committed to long-term follow-up see page 676). Relapse occurring after observation essentially represents a prolongation in treatment lead time. Therefore, these patients are treated according to the stage at relapse. Radiotherapy is generally not given to patients at higher risk for resultant morbidity, such as those with stages IA and IB with a horseshoe or pelvic kidney, with inflammatory bowel disease, and who underwent prior radiotherapy.

Follow-up includes a history and physical, with measurement of serum tumor markers, performed every 3 to 4 months for the first year, every 6 months for the second year, and annually thereafter. More intense follow-up is recommended for patients not undergoing radiotherapy. A history and physical, with measurement of serum tumor markers, should be performed every 3 to 4 months for the first 3 years, every 6 months for the next 3 years, and annually thereafter. An annual pelvic CT is recommended for 3 years in patients who underwent para-aortic radiotherapy, whereas an abdominal/pelvic CT scan is recommended at each visit and chest radiograph at alternate visits for up to 10 years for those treated with a single dose of carboplatin or those undergoing surveillance.

Stage IS

Patients with stage IS disease are treated with radiation (25–30 Gy) to the infradiaphragmatic area, including para-aortic lymph nodes with or without radiation to the ipsilateral ileoinguinal nodes.[4] Follow-up recommendations are similar to those for patients with stages 1A and 1B disease. If advanced disseminated disease is suspected, than a full course of chemotherapy is administered according to the guidelines for good-risk GCT.

Stages IIA and IIB

Stage IIA is defined as disease measuring less than 2 cm in diameter on CT scan, and stage IIB as disease measuring 2 to 5 cm in maximum diameter. For patients with stage IIA or IIB disease, 35 to 40 Gy is administered to the infradiaphragmatic area, including para-aortic and ipsilateral iliac lymph nodes. As in the management of stage I disease, prophylactic mediastinal radiation therapy is not indicated.[8]

Surveillance is not an option for patients with stage IIA or IIB disease with relative contraindications for radiation. Instead, 4 courses of etoposide and cisplatin (EP) are recommended.

Follow-up for patients with stage IIA or IIB disease includes a history and physical, with measurement of serum tumor markers, should be performed every 3 to 4 months for the first 3 years, every 6 months for the fourth year, and annually thereafter. Abdominal CT is recommended after 4 months during the first year (see page 676).

Stages IIC and III

Patients with stage IIC or III disease are those considered at good or intermediate risk (see page 676). All stage IIC and III disease is considered good risk except for stage III disease with nonpulmonary visceral metastases, which is considered intermediate-risk (see page 683). Although standard chemotherapy is used for both groups of patients, for patients with good risk, either 4 cycles of EP or 3 cycles of bleomycin, etoposide, and cisplatin (BEP) are recommended. In contrast, 4 cycles of BEP are recommended for those with intermediate-risk disease. These options are all considered category 1 recommendations.[9–12]

After initial chemotherapy, patients with stage IIC and III are evaluated with serum tumor markers and a CT scan of the chest, abdomen, and pelvis (see page 677). Patients are then classified according to the presence or absence of a residual mass and the status of serum tumor markers. Patients with no residual mass and normal markers need no further treatment and undergo surveillance. For patients with a residual mass and normal markers, a PET scan is recommended to assess for residual viable tumor.[13] To reduce the incidence of false-positive results, the PET scan is typically performed no fewer than

6 weeks after completion of chemotherapy. Notably, granulomatous disease, such as sarcoid, is a frequent source of false-positive results. If the PET scan is negative, no further treatment is needed, but the patient should be observed closely for recurrence. If it is positive, then biopsy should be considered followed by surgical excision (category 2B) or salvage therapy. Alternatively, the patient can be treated with radiotherapy (category 2B).

For patients who cannot undergo a PET scan, postchemotherapy management is based on CT scan findings. Controversy exists regarding optimal management when the residual mass is greater than 3 cm, because approximately 25% of these patients have a viable seminoma or previously unrecognized nonseminoma.[14] Options include surgery (category 2B), radiotherapy (category 2B), and observation.[8] If surgery is selected, the procedure consists of resection of the residual mass or multiple biopsies. A full bilateral or modified retroperitoneal lymph node dissection (RPLND) is not performed because of its technical difficulty in patients with seminoma and because of extensive fibrosis, which may be associated with severe morbidity.[15] If the residual mass is 3 cm or less, patients should undergo observation, which is detailed in the algorithm (see page 677).

Recurrent disease is initially treated according to the stage at recurrence. Salvage therapy is recommended for patients with rising markers or a growing mass detected on CT scan (see page 682). Salvage therapy for seminoma and nonseminoma is similar and is discussed further in the next section on nonseminomas.

Patients with seminoma arising from an extragonadal site, such as the mediastinum, are treated with standard chemotherapy regimens according to risk status. Approximately 90% of patients with advanced seminoma are cured with cisplatin-containing chemotherapy.[16]

Nonseminoma

The risk classification for nonseminoma is defined on page 683. Stage-dependent treatment options after inguinal orchiectomy include observation, chemotherapy, and RPLND. Although the timing of the RPLND may vary, most patients with nonseminoma will undergo an RPLND for either diagnostic or therapeutic purposes at some point during treatment. The major morbidity associated with bilateral dissection is retrograde ejaculation, resulting in infertility. Nerve-dissection techniques preserve antegrade ejaculation in 90% of cases.[17] Template dissections, which avoid the contralateral sympathetic chain, postganglionic sympathetic fibers, and hypogastric plexus, preserve ejaculation in approximately 80% of patients.

In general, an open nerve-sparing RPLND rather than a laparoscopic RPLND is recommended for therapeutic purposes. For example, a concern exists that laparoscopic RPLND may result in false-negative results caused by inadequate sampling, and no published reports focus on the therapeutic efficacy of a laparoscopic dissection. Because the recommended number of chemotherapy cycles is based on the number of positive nodes identified, inadequate sampling may lead to partial treatment.[18]

Stage IA

Two management options exist for patients with stage IA disease after orchiectomy: 1) surveillance (in compliant patients) and 2) open nerve-sparing RPLND (see page 678).

The cure rate with either approach exceeds 95%. However, the high cure rate associated with surveillance depends on adherence to periodic follow-up examinations and subsequent chemotherapy for the 20% to 30% of patients who experience relapse. Follow-up examinations in those electing surveillance include an abdominopelvic CT scan every 2 to 3 months for the first year, and every 3 to 4 months during the second year. Serum marker determination and chest radiograph should be performed every 1 to 2 months during the first year and every 2 months during the second year (see page 681). Noncompliant patients are treated with open RPLND.

The open nerve-sparing RPLND is typically performed within 4 weeks of a CT scan and within 7 to 10 days of repeat serum marker testing to ensure accurate presurgical staging. If the dissected lymph nodes are not involved with a tumor (pN0), no adjuvant chemotherapy is given after open nerve-sparing RPLND. However, if the resected lymph nodes involve tumor, the decision whether to use adjuvant chemotherapy is based on the degree of nodal involvement and the patient's ability to comply with surveillance (see page 679). Chemotherapy is preferred over surveillance in patients with pN2 or pN3 disease. Recommended regimens include either EP

or BEP; 2 cycles of either regimen are recommended for patients with pN1 or pN2 disease, with 4 cycles of EP and 3 cycles of BEP (preferred) for patients with pN3 disease.

Stage IB

Open nerve-sparing RPLND is a treatment option in patients with stage IB disease, and the subsequent adjuvant therapy options are similar to those for stage IA. Chemotherapy with 2 cycles of BEP (category 2B) followed by open nerve-sparing RPLND or surveillance is another option (see page 679). Finally, surveillance alone may be offered to compliant patients with T2 disease (category 2B; see page 678). Vascular invasion is a significant predictor of relapse when orchiectomy is followed by surveillance alone.[2] Surveillance is generally not recommended for T2 disease with vascular invasion because of the 50% chance of relapse. Exceptions are made according to individual circumstances in compliant patients. When surveillance is opted in selected patients with T2 disease, both the patient and physician must be compliant with follow-up recommendations.

Stage IS

Patients with stage IS disease exhibit a persistent elevation of markers but no radiographic evidence of disease. These patients are treated with standard chemotherapy with either 4 cycles of EP or 3 cycles of BEP (see page 678). Either regimen is preferable to initial open nerve-sparing RPLND because these patients nearly always have disseminated disease.[19,20]

Stages IIA and IIB

Treatment for patients with stage IIA nonseminoma depends on serum tumor marker levels. When the levels of tumor markers are persistently elevated, patients are treated with chemotherapy (4 cycles of EP or 3 cycles of BEP), followed by open nerve-sparing RPLND or surveillance (see page 678).

When the tumor marker levels are negative, 2 treatment options are available. Patients can undergo primary chemotherapy with 4 cycles of EP or 3 cycles of BEP (category 2B), followed by open nerve-sparing RPLND or surveillance (see page 678).[21] This treatment is considered particularly appropriate if the patient has multifocal disease. Alternatively, the patient can undergo open nerve-sparing RPLND followed by adjuvant chemotherapy or surveillance, depending on the number of positive lymph nodes identified and patient compliance (see page 679). For example, surveillance is preferred in compliant patients with pN1 disease, whereas chemotherapy is preferred for pN2 disease and surveillance is not recommended for pN3 disease. Recommended chemotherapy consists of 2 cycles of BEP or EP, resulting in a nearly 100% relapse-free survival rate.[22]

Treatment for patients with stage IIB disease depends on both tumor marker levels and radiographic findings (see page 678). When tumor markers are negative, CT findings determine the proper course of treatment. If abnormal radiographic findings are limited to sites within the lymphatic drainage (i.e., landing zone), 2 management options are available. One option is to perform open nerve-sparing RPLND and consider adjuvant chemotherapy as described for patients with stage IIA disease (page 679). The second option is to treat these patients with primary chemotherapy with 4 cycles of EP or 3 cycles of BEP, followed by open nerve-sparing RPLND or surveillance (page 679). If metastatic disease (based on radiographic findings) is not confined to the lymphatic drainage (i.e., multifocal lymph node metastases outside lymphatic drainage sites), similar primary chemotherapy is recommended and initial open RPLND is not.

Stages IIC and III

Patients with stage IIC and III disease are treated with primary chemotherapy regimens based on risk status (page 683). Also, patients with an extragonadal primary site, whether retroperitoneal or mediastinal, are treated with initial chemotherapy. Classifications of risk status emerged from chemotherapy research designed to decrease the toxicity of the regimens while maintaining maximal efficacy.

Initial chemotherapy combinations studied in the 1970s contained cisplatin, vinblastine, and bleomycin and achieved a complete response in 70% to 80% of patients with metastatic GCTs. These regimens were associated with serious adverse effects, including neuromuscular toxic effects, death from myelosuppression or bleomycin-induced pulmonary fibrosis, and Raynaud's phenomenon.

The high cure rate and toxicity associated with cisplatin, vinblastine, and bleomycin regimens resulted in efforts to stratify patients and tailor therapy according to risk. Extent of disease and serum tumor markers were identified as important prognostic features, and models were developed to stratify patients into good- and poor-risk categories.

The International Germ Cell Cancer Consensus Classification incorporated the risk groups into the American Joint Committee on Cancer staging for GCTs (see staging table, available online, in these guidelines, at www.nccn.org [ST-1]). This classification categorized patients as good-, intermediate-, or poor-risk.[23]

Good-Risk (Stages IIC and IIIA) Nonseminoma

Treatment programs for good-risk GCTs were designed to decrease toxicity while maintaining maximal efficacy. Randomized clinical trials showed that this was achieved by substituting etoposide for vinblastine,[24,25] and either eliminating or reducing the dose of bleomycin.[25,26] Presently, 2 regimens are considered standard treatment programs in the United States for good-risk GCTs: 4 cycles of EP or 3 cycles of BEP (see page 684). Either regimen is well tolerated and cures approximately 90% of patients with good risk.[27]

Intermediate- (Stage IIIB) and Poor-Risk (Stage IIIC) Nonseminoma

Between 20% and 30% of all patients with metastatic GCTs are not cured with conventional cisplatin therapy. Poor prognostic features at diagnosis used to identify these patients include nonpulmonary visceral metastases and high serum tumor marker concentrations or mediastinal primary site in patients with nonseminoma.[28] In patients with these prognostic factors, clinical trials are directed at improving efficacy.

For patients with intermediate-risk nonseminoma, the cure rate is approximately 70% for standard therapy with 4 cycles of BEP. In patients with poor-risk GCTs (stage IIIC), fewer than one half experience a durable complete response to 4 cycles of BEP, and therefore treatment in a clinical trial is preferred.[28] The panel recommends 4 cycles of etoposide, iphosphamide, and cisplatin (VIP) for patients who may not tolerate bleomycin.[29]

Primary chemotherapy plus radiotherapy is indicated for patients in whom brain metastases are detected. If clinically indicated, surgery should also be performed.

Postchemotherapy Management for Stages IIC and IIIA–IIIC Nonseminoma

At the conclusion of induction chemotherapy, CT scans of the abdomen and pelvis are indicated, along with serum tumor marker assays. PET scans for residual disease have limited predictive value. If a complete response is found and the tumor markers are negative, 2 management options exist: surveillance (category 2B) or open nerve-sparing RPLND (category 2B).

If residual disease is found and the serum tumor markers have normalized, then all sites of residual disease are resected. If only necrotic debris or mature teratoma is encountered, no further therapy is necessary and standard observation is initiated. In the 15% of patients who have viable residual cancer, 2 cycles of chemotherapy (EP, VelP [paclitaxel/ifosfamide/cisplatin], or TIP [vinblastine/ifosfamide/cisplatin]) are administered.

After patients are rendered disease-free, standard observation is initiated (see page 681). Patients who experience an incomplete response to first-line therapy or unresectable disease at surgery are treated with salvage therapy (see page 682).

Salvage Therapy

Patients who do not experience a complete response to first-line therapy are divided into those with a favorable or unfavorable prognosis (see page 682). Favorable prognostic factors include a testicular primary site, prior complete response to first-line therapy, low levels of serum markers, and low-volume disease.[30] Standard therapy for patients with these features is 4 cycles of cisplatin and ifosfamide combined with vinblastine or paclitaxel (see page 685). Approximately 50% of patients treated with the vinblastine regimen experience a complete response, and 25% experience durable complete remission.[31,32] If patients experience an incomplete response or relapses after salvage chemotherapy, high-dose chemotherapy with autologous stem cell support is the preferred option. Surgical salvage should be considered if a single site of metastasis is present and resectable. Other options are participation in a clinical trial or best supportive care.

Patients with unfavorable prognostic features for conventional-dose salvage therapy (e.g., incomplete response to first-line therapy) and those requiring third-line salvage therapy are considered for treatment with high-dose chemotherapy plus autologous stem cell support (category 2B), participation in a clinical trial (preferred), or best supportive care. Third-line therapy with 2 cycles of high-dose carboplatin plus etoposide, with or without cyclophospha-

mide (or ifosfamide), results in a durable complete response in 15% to 20% of patients.[33]

For patients being considered for treatment with a high-dose program, prognostic factors are used in deciding treatment. Patients with a testicular primary site and rising markers during first-line therapy are considered for high-dose programs as second-line therapy. Predictors of poor outcome to high-dose carboplatin-containing chemotherapy include a high serum hCG concentration, mediastinal primary site, and insensitivity to cisplatin (absolute refractory disease).[34] Patients with these features are generally spared the morbidity of this therapy and are considered for investigational therapy or surgical resection, particularly patients with a mediastinal primary or single site of metastasis.

For patients who do not experience complete response to high-dose therapy, the disease is nearly always incurable; the only exception is the rare patient with elevated serum tumor markers and a solitary site of metastasis (usually retroperitoneal) that undergoes surgical resection.[35] All other patients should be considered for palliative outpatient chemotherapy or radiation therapy. A recommended palliative second-line salvage therapy for patients with intensively pretreated, cisplatin-resistant, or refractory GCT is the combination of gemcitabine with oxaliplatin (GEMOX; category 2A recommendation). This recommendation is based on data from phase II studies.[36–38] These studies investigated the efficacy and the toxicity of GEMOX in patients with relapsed or cisplatin-refractory GCTs. Toxicity was found to be primarily hematologic and generally manageable. The results showed that GEMOX is a safe for patients with cisplatin-refractory testicular GCTs and may offer a chance of long-term survival.[36–38]

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Individual Disclosures of the NCCN Testicular Cancer Panel

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